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című program

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Investigating the epidemiological factors, efficacy and side effect profile of emergency contraception

PhD thesis

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LIST OF ABBREVATIONS

BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
COC	Continuous contraception
DES	Diethylstilbestrol
EC	Emergency contraception
EE	Ethinyl estradiol
FDA	Food and Drug Administration
IUD	Intrauterine Device
IUS	Intrauterine System
LAM	Lactation amenorrhea method
LARC	Long-Acting Reversible Contraception
LH	Luteinizing hormone
LNG	Levonorgestrel
MEEC	Motivation and Epidemiology of Emergency Contraceptive Pill
OAC	Oral contraceptive
RCT	Randomized controlled trials
SPRM	Selective progesterone receptor modulator
SHBG	Sex hormone-binding globulin
STDs	Sexually Transmitted Diseases
UPA	Ulipristal acetate
WHO	World Health Organization

1. INTRODUCTION

1.1. Unintended pregnancy

Over half of all pregnancies are unintended, resulting in a substantial global burden of induced abortions, as reported by the World Health Organization (WHO) (1). To mitigate this, it is essential to have a comprehensive understanding of contraceptive methods and their effective utilization. Particularly, emergency contraception (EC) plays a pivotal role as an easily accessible option for preventing unintended pregnancies. By employing emergency contraception and promoting awareness of postcoital contraception, the incidence of unintended pregnancies could potentially decrease by 75% (2).

Emergency contraception refers to a form of contraception, such as pills or intrauterine device (IUD), that is utilized to prevent unintended pregnancies following unprotected sexual intercourse.

Apart from primary preventive methods of contraception, postcoital contraceptive methods are employed after intercourse but prior to embryo implantation. These methods serve to enhance protection on an occasional basis and should not be regarded as the standard means of contraception (3).

1.2. Emergency Contraceptive Methods

1.2.1. Emergency contraceptive pills

The emergency contraceptive pills primarily work by delaying or inhibiting ovulation, but their mechanism of action is not limited to that. They may also have an impact on sperm function, preventing fertilization, and can affect the lining of the uterus, making it less receptive to implantation.

There are different types of emergency contraceptive pills available. The most widely used variant contains levonorgestrel, a synthetic hormone that mimics progesterone. Another type of emergency contraceptive pill is formulated with ulipristal acetate, which acts as a selective progesterone receptor modulator.

The effectiveness of emergency contraceptive pills decreases with time, and the levonorgestrel-containing pill is most effective when taken within 72 of unprotected

intercourse. While ulipristal acetate can be taken up to 120 hours after intercourse, its efficacy diminishes as the time frame extends.
It's important to note that they do not induce abortion.

1.2.2. Emergency contraceptive intrauterine device

Emergency contraceptive IUDs are one of the most effective forms of emergency contraception. IUDs besides that they are preventing unintended pregnancy, they have a minimal risk of failure and long-lasting contraceptive protection.
Emergency contraceptive intrauterine devices offer a hormone-free option for individuals seeking contraception. Emergency contraceptive IUDs, like the Copper IUD do not contain hormones, which makes them a favorable choice for those who favor contraception methods that do not involve the use of hormones. Copper IUDs, prevent fertilization through chemical alterations in sperm and eggs, as well as by impeding implantation.
IUDs can be inserted up to 120 hours after unprotected intercourse and they not only serve as emergency contraception but also function as highly effective long-term contraceptive options. Once inserted, they can provide continuous contraception for an extended period, typically spanning several years, depending on the specific type of IUD chosen.

1.2.3. Choosing emergency contraceptive method

On a global scale, it is estimated that approximately 5.9 million unintended pregnancies occur due to contraceptive failure when methods are used perfectly. However, when methods are used in a typical manner, the number of unintended pregnancies significantly rises to 26.5 million. These statistics highlight the importance of using contraceptives consistently and correctly to reduce the risk of unintended pregnancies (4).
Emergency contraception is a crucial method available to women in cases where their regular contraception has failed or when they have engaged in unprotected sexual intercourse. However, it should be emphasized that EC is not a replacement for consistent and proper use of regular contraception methods.

2. OBJECTIVES

The use of emergency contraceptives can be influenced by several epidemiological factors. Age, socioeconomic status, education level, and relationship status can play a role in the use of emergency contraception.

Our current knowledge regarding the impact of personal factors and sexual behaviors on the utilization of emergency contraception is limited. Many people are uninformed about the specific details related to emergency contraception, such as the types available, the timeframe within which it can be used, potential side effects, and where to access it.

It is crucial to emphasize that the limited understanding and awareness pertaining to emergency contraception can have far-reaching consequences on individuals' capacity to make well-informed choices regarding their reproductive health and effectively access suitable healthcare services when the need arises.

Existing studies examining this relationship have predominantly focused on specific demographic groups or age brackets, utilizing retrospective surveys that guarantee anonymity. It's crucial to acknowledge that although certain overarching patterns have been identified, the utilization of emergency contraception is subject to a multitude of individual, cultural, and contextual factors that may not have been fully accounted for in current research. Consequently, there remains a considerable amount of knowledge to be gained regarding the intricate dynamics and interconnections between epidemiological variables and women's choices concerning the adoption of emergency contraception.

We aimed:

1) to provide an up-to-date overview of the previously and currently used methods of emergency contraception, their effectiveness, and practical application;
2) to investigate the elucidation and comprehension the factors that promote women to seek emergency contraception immediately after intercourse.

3. METHODS

3.1. Emergency contraception- systematic review of the literature

3.1.1. Literature search and study selection in the systematic review

For this literature review, we conducted a systematic literature search using the MEDLINE (PubMed), Embase, and Scopus databases, following the methodology employed in previous systematic literature reviews published in the Orvosi Hetilap (5, 6). The search was limited to clinical publications in English and Hungarian languages, independently performed by two reviewers, covering the period between 1960 and 2023. The literature search was conducted using predetermined MeSH-compatible keywords and phrases (such as "emergency contraceptive" or "emergency contraception" or "oral emergency contraception" or "mifepristone" or "morning after-pill" or "postcoital contraceptives" or "hormonal postcoital contraceptive" or "progestin-only pill" or "ulipristal acetate" or "intrauterine device" or "IUD" or "Cu-IUD" or "LNG-IUD" or "Copper IUD" or "IUD in emergency" or "synthetic postcoital contraceptive") (Figure 1). Editorials and letters were excluded due to their low level of evidence. Studies conducted without ethical approval were not included in the analysis.

Following the exclusion of duplicates, title and abstract screening were performed, followed by full-text retrieval. Manuscripts in languages other than English and Hungarian, studies involving non-human models, and publications comparing emergency contraceptives with long-term contraceptives were excluded.

3.1.2. Methodological evaluation of the studies in the systematic review

The examined studies were evaluated based on various methodological criteria. The criteria we considered were as follows:

a) Clearly defined study objectives.

b) Adequate sample size for drawing statistical conclusions.

c) Sufficiently informative follow-up period (at least 1 month).

d) Primary outcome variables included the Pearl Index or the number of pregnancies despite medication.

e) The studies provided detailed information on adverse events and side effect profiles.

3.2. Retrospective observational study - Motivators for emergency contraception

3.2.1. Patients in the Hungarian database

The MEEC (Motivation and Epidemiology of Emergency Contraceptive Pill) contains this retrospective observational study, which is based on a Hungarian data bank's study cohort that includes follow-up information on 455 women. A total of 455 people enrolled on the telemedicine consultation portal "esemenyutan.hu" between July 2021 and September 2021. People could obtain an emergency contraception prescription after speaking with a gynecologist. Each patient was asked to respond to a series of standard questions about their sexual habits and way of life during the session.

3.2.2. Characteristics

The following factors were included in this study, which was based on a review of all of these patients' charts: age (determined by deducting the date of consultation from the date of birth) and relationship status (married, in a relationship, or single).

The following gynecological details were also included in the questionnaire: the year of the last Pap smear; the first day of the last menstrual period and the number of days since the last menstrual period; the number of pregnancies, abortions, and miscarriages; and the description of the intercourse (including the precise day and hour of the intercourse, the time elapsed between the registration and the intercourse, and the method of contraception).

The Semmelweis University Institutional Review Board gave their approval to the study (SE RKEB: 125/2022).

3.2.3. Data management

The data were checked for inaccuracies in data entry and repeated consultations (two visits total; only the first visit was retained).

Aged over vs. below thirty years was the binary age variable that was created. Depending on whether the sexual encounter occurred later in the cycle or close to ovulation, the patients were categorized into groups. Given that the cycle was regular and lasted roughly

28 days, the period's 12–16 days were considered to be the vicinity to ovulation. The three groups of contraception methods were: condom use, no contraception at all, and other (which may include any oral contraceptive (OAC) with days missed, a contraceptive ring that had been out for too long, or an unsuccessful attempt to stop having sex).

3.2.4. Statistical analysis

To check if continuous variables were normal, the Shapiro-Wilk test was employed. Since that none of the variables had a normal distribution, continuous data were expressed as medians and interquartile ranges. The time since the last sex was compared to age, relationship status, history of pregnancies, history of abortions, and proximity to ovulation using the Mann-Whitney test. To determine the link between the method of contraception and age, relationship status, history of pregnancies, history of abortions, and closeness to ovulation, chi-square analysis was used. The connections between the dependent variable (time) and the independent factors (age, protection (yes/no), ovulation time, history of pregnancies (yes/no), being in a relationship (yes/no), and protection) were predicted using multivariate logistic regression analysis. If the patients registered on the website within 24 hours, the dependent variable (time) obtained a value of 1, and if it was more than 24 hours, it received a value of 0.

At $p<0.05$, statistical significance was established. The programs SPSS Sigma Stat and Prism9 GraphPad (ver. 8, GraphPad Software, Inc., San Diego, CA, USA) were used for figure creation, data management, and analysis.

4. RESULTS

4.1. Emergency contraception- systematic review of the literature

4.1.1. Search results of systematic review

As a result of the keyword search, we found 8933 studies. After the elimination of duplicates and the selection based on title and abstract, we further examined 135 relevant studies. Out of these, we excluded an additional 112 studies from our review due to incomplete information on drug treatment. Finally, we included 23 clinical trials in our systematic literature review **(Figure 1)**.

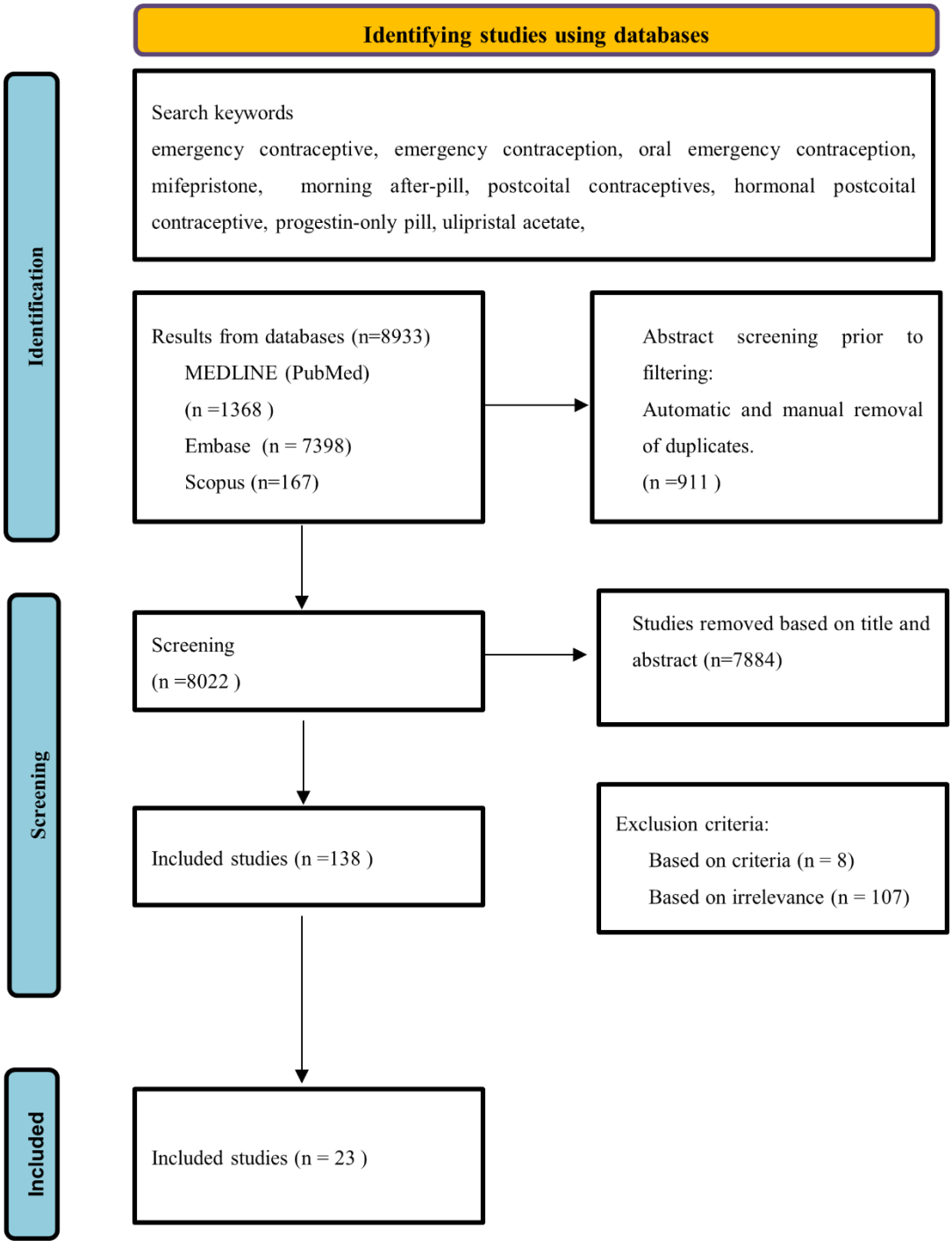

Figure 1. The flowchart of the systematic literature search process (7).

Table 1 and 2 contains the methodology of the selected publications.

Table 1.: The methodology of the studies I. (7)

* Investigation of the effect on lactation.

First Author	Year	Study design	Investigated preparation	Time elapsed since the event (hours)	Number of the patients (n)
Arowojolu (8)	2002	RCT	LNG (2x0.75 vs 1.5 mg)	72	1118
Bhatia (9)	2011	Retrospective Cohort	Copper vs LNG (2x0.75 mg)	120 vs 72	68
Changhai (10)	2002	RCT	Mifepristone vs Mifepristone + Tamoxifen	120	400
Creinin (11)	2006	RCT	UPA vs LNG	72	773
D'Souza (12)	2003	RCT	GyneFix vs Copper	X	175
Dada (13)	2010	RCT	LNG (2X0.75 VS 1-5 mg)	72	3022
Festin (14)	2016	Multicenter prospective cohort Phase III trial	LNG (1,5 mg)	Before or within 24 hours of each intercourse	330
Fine (15)	2010	Retrospective Cohort	UPA	120	1241
Glasier (16)	1992	RCT	Mifeprisone vs Yuzpe	72	800
Glasier (17)	2010	RCT	UPA vs LNG	120	2221
Ho (18)	1993	RCT	Yuzpe vs LNG	48	834
Kuchera (19)	1971	Retrospective Cohort	Diethylstilbestrol	72	1000
Moreau (20)	2012	Prospective, multicenter	UPA	120	2183
von Hertzen (21)	1999	RCT	Mifepriston	120	1717
Polakow-Farkash (22) *	2013	Prospective cohort	LNG	X	143
Sääv (23)*	2010	Retrospective Cohort	Mifepristone	X	12

First Author	Year	Study design	Investigated preparation	Time elapsed since the event (hours)	Number of the patients (n)
Shabaan (24) *	2013	RCT	LNG	120	1158
Szontagh (25)	1969	Clinical trial	Dienesztrol	X (after intercourse)	30
Turok (26)	2014	Observational study	Copper vs LNG	120	548
Turok (27)	2021	RCT	Copper vs LNG IUS	120	711
Van Santen (28)	1985	Retrospective Cohort	Yuzpe	24	633
Yuzpe (29)	1982	Retrospective Cohort	Yuzpe	72	692
Zhou (30)	2001	Multicenter retrospective cohort	Copper	120	1013

Table 2.: The methodology of the studies II. (7)

* Investigation of the effect on lactation.

First Author	Year	Investigating of effectiveness	Follow-up	Randomization and its description	Statistical analysis
Arowojolu (8)	2002	✓	✓	✓	✓
Bhatia (9)	2011	✓	✓	X	Descriptive statistics
Changhai (10)	2002	✓	✓	✓	✓
Creinin (11)	2006	✓	✓	✓	✓
D'Souza (12)	2003	✓	✓	✓	✓
Dada (13)	2010	✓	✓	✓	✓
Festin (14)	2016	✓	✓	✓	✓
Fine (15)	2010	✓	✓	X	Descriptive statistics
Glasier (16)	1992	✓	✓	✓	✓
Glasier (17)	2010	✓	✓	✓	✓
Ho (18)	1993	✓	✓	✓	✓
Kuchera (19)	1971	✓	✓	X	Descriptive statistics

First Author	Year	Investigating of effectiveness	Follow-up	Randomization and its description	Statistical analysis
Moreau (20)	2012	✓	✓	X	✓
von Hertzen (21)	1999	✓	✓	✓	✓
Polakow-Farkash (22) *	2013	✓	✓	X	✓
Sääv (23)*	2010	✓	X	X	Descriptive statistics
Shabaan (24) *	2013	✓	✓	✓	✓
Szontagh (25)	1969	✓	✓	X	Descriptive statistics
Turok (26)	2014	✓	✓	X	✓
Turok (27)	2021	✓	✓	✓	✓
Van Santen (28)	1985	✓	✓	X	Descriptive statistics
Yuzpe (29)	1982	✓	✓	X	Descriptive statistics
Zhou (30)	2001	✓	✓	X	✓

These 23 studies, that we have selected cover the entire spectrum (Dienestrol, Diethylstilbestrol, Levonorgestrel, Mifepristone, Mifepristone+Tamoxifen, Ulipristal acetate, Yuzpe-protocol, Copper IUS, GyneFix, LNG-IUS) of emergency contraceptives. Some studies analyzed the effectiveness of oral emergency contraceptives, while several studies gave a scientific treatise on the Copper-IUD.

The postcoital contraceptive methods (in these 23 studies) are contained in Table 3, while the emergency contraceptive methods available in Hungary are listed in Table 4.

Table 3.: Postcoital contraceptive methods (7)

* According to the FDA recommendation, the following hormone combinations can be used according to the Yuzpe protocol: levonorgestrel 0,15 mg/ ethinylestradiol 30 mg; levonorgestrel 0,1 mg/ ethinylestradiol 20 mg; norgestrel 0,5 mg/ ethinylestradiol 50 mg (22).

Investigated preparation	First auther	Side effect profile	Summary
Copper IUS	Bhatia (9) D'Souza (31) Turok (26) Turok (27) Zhou (30)	Bleeding abnormalities, pelvic discomfort	It can be inserted up to 5 days after intercourse. Their advantage is that they provide long-term contraception after insertion. The FDA does not have approval for such indication of use.
Dienestrol	Szontagh (25)	Nausea, chest discomfort, and abnormal bleeding	A close analogue of Diethylstilbestrol, a synthetic estrogen. It is not approved by the FDA for use as emergency contraception.
Diethylstilbestrol (not available on the market)	Kuchera (19)	Severe nausea, vomiting, headache, and abnormal bleeding	DES (Diethylstilbestrol) is a synthetic estrogen that inhibits implantation. Its teratogenic effects cannot be ruled out. The recommended dosage is 25 mg twice daily for 5 days. Due to its carcinogenic properties, it has been banned by the FDA.
GyneFix	D'Souza (31)	More painful insertion compared to a traditional IUS.	Compared to the insertion of a Copper IUD, there is greater discomfort but fewer long-term side effects. The FDA does not have approval for such indication of use.
Levonorgestrel	Arowojolu (8) Bhatia (9) Creinin (11) Dada (13) Festin (14) Glasier (32) Ho (18) Polakow-Farkash (22)	Headache, breast tenderness, and heavy menstrual bleeding	It is approved in Hungary and available in both 1x1.5 mg and 2x0.75 mg formulations, with no difference in terms of efficacy. It is well-tolerated and widely accessible medication.

Investigated preparation	First auther	Side effect profile	Summary
	Shabaan (24) Turok (26)		
LNG-IUS	Turok (27)	It has a similar side effect profile compared to copper.	It provides protection against unintended pregnancy even 6-14 days after intercourse. Its insertion offers long-term protection. It does not have FDA approval for this indication.
Mifepristone	Changhai (10) Glasier (16) von Hertzen (21) Sääv (23)	Delay in menses	Compared to Mifeproistone 600 mg, the Yuzpe protocol has fewer side effects. Comparing 600, 50, and 10 mg packages, the same effectiveness could be verified. Compared to LNG, it did not prove to be more efficient.
Mifepristone + Tamoxifen	Changhai (10)	Nausea, fatigue	Compared to mifepristone, the effectiveness is the same, with a statistically non-significant difference in terms of side effects.
Ulipristal acetate	Creinin (11) Fine (15) Glasier (17) Moreau (20)	Pelvic pain, dysmenorrhea	Post-event tablet approved in Hungary and usable up to 120 hours after the event.
Yuzpe-protocol*	Glasier (16) Ho (18) Van Santen (28) Yuzpe (29)	Headache, nausea, vomiting, breast tenderness	It is safe to use against the teratogenicity of DES. Initially, it involved taking 200 mcg of ethinyl estradiol and 2 mg of di-norgestrel within 72 or 120 hours after intercourse. This has been modified to 100 mcg of ethinyl estradiol and 1 mg of di-norgestrel. It has a strong side effect profile.

Table 4. Emergency contraceptive methods available in Hungary (7).

Name of active substance	Product name	Time frame	Efficacy	Side effect	Disadvantage
Ethinylestradiol and LNG (Yuzpe - protocol)	There is no finished product. *	72 hours		-Strong estrogen side effects - nausea, vomiting	Combination of medications is necessary to achieve the desired dose
LNG	*Escapelle* (1,5 mg Single-dose *Rigesoft* (2x 0,75 mg)	72 hours		-Nausea; -Bleeding after intake; -Headache	Effectiveness decreases over time
Ulipristal-acetate	*EllaOne* (30 mg)	120 hours		-Nausea, abdominal pain or discomfort, vomiting; -Painful menstruation, pelvic pain, breast pain; -Headache, -Muscle pain, back pain, fatigue	More difficult accessibility (available in fewer pharmacies)
Hormone-free intrauterine device (IUD)	for example: *Goldlily/ Gold T*	120 hours		-Pelvic discomfort	Insertion requires a medical visit; Price exceeds that of orally taken options.

4.1.4. The efficacy of emergency contraceptive protocols

Although Yuzpe preparations are not available in Hungary, it is important to mention that the pregnancy rate in the studies we reviewed ranged from 1.2% to 2.6% for the Yuzpe protocol (18, 28, 29).

For LNG, both the studies with two doses of 0.75 mg and the studies with a single dose of 1.5 mg were included in the systematic review. Some studies found a significantly lower estimated efficacy rate for the lower dose of LNG (86.8%) compared to the higher dose (92.99%) (8). However, other studies did not find a difference in efficacy (risk difference of 0.7%) (13). The pregnancy rate ranged from 0.57% to 1% in the examined studies (8, 13), indicating that LNG was more effective than Yuzpe. It is important to note, however, that using LNG multiple times within one menstrual cycle (1.5 mg LNG

after each intercourse, up to a maximum of 6 times) significantly increases the pregnancy rate, with a pregnancy rate of 4.4% in typical use (14).

For mifepristone, the pregnancy rate was around 1%, and there was no difference in efficacy when compared to LNG or the combination of mifepristone and tamoxifen in the studies we reviewed (10, 21). When comparing mifepristone with the Yuzpe protocol, the pregnancy rate was 0% for mifepristone and 1% for Yuzpe (not significantly different) (16).

UPA proved to be more effective than LNG: 85% of pregnancies were avoided with the use of UPA, compared to 69% with LNG (11). Furthermore, the pregnancy rate was 1.8% for UPA and 2.6% for LNG (17). The effectiveness of UPA does not decrease with an increase in time (48 vs 120 hours) (15).

Table 5 summarizes the effectiveness of emergency contraception.

Table 5. Effeciacy of emergency contraceptives (7)

First author **Study design** **Investigated preparation**	**Efficacy**
Arowojolu (8) RCT LNG (2x0.75 vs 1.5 mg)	The relative risk of pregnancy was similar in both groups (RR 9.71, 95% CI 0.32-1.55, p<0.05). However, the estimated efficacy rate in the lower dosage group (86.8%) was significantly lower than the estimated efficacy rate in the higher dosage group (92.99%).
Bhatia (9) Retrospective Cohort Copper vs LNG (2x0.75 mg)	There was no difference in efficacy between the two methods used.
Changhai (10) RCT Mifepristone vs Mifepristone + Tamoxifen	The rate of women who became pregnant was lower with combined treatment compared to treatment with only mifepristone (0% vs. 2%), although the difference did not reach statistical significance. With the Trussel method, the prevention rate of pregnancies was 84% with only mifepristone and 95% with combined treatment, which also did not show a significant difference.
Creinin (11) RCT UPA vs LNG	In cases of UPA (ulipristal acetate), pregnancy occurred in 0.9% (95% CI 0.2-1.6%) of cases, while with LNG (levonorgestrel) it occurred in 1.7% (95% CI 0.8-2.6%) of cases. Based on the estimated cycle day of unprotected intercourse, UPA was able to prevent approximately 85% of expected pregnancies, while LNG prevented approximately 69%.
D'Souza (31) RCT GyneFix vs Copper	The insertion of GyneFix was more painful than Copper. Following the insertion of GyneFix, there was significantly less abdominal pain in the 30 days compared to Copper. 13% of women requested removal due to pain with GyneFix, compared to 20% with Copper.
Dada (13) RCT LNG (2x0,75 vs 1,5 mg)	There was no difference in efficacy between the twice 0.75 mg dose and the 1.5 mg dose: the rate of post-treatment pregnancy was 0.57% for the two-dose treatment and 0.64% for the single dose (risk difference 0.07%, 95% CI -0.05-0.64).
Festin (14) Multicenter Prospective	Follow-up: 2.5, 4.5, and 6.5 months 330 (321) women Before or within 24 hours of intercourse. 7.1 (95% CI 3.8-13.1) pregnancies per 100 woman-years with typical use.

First author Study design Investigated preparation	Efficacy
Cohort 1,5 mg LNG after each intercourse (up to a maximum of 6 times per month) Phase III trial	7.5 (95% CI 4.0-13.9) pregnancies per 100 woman-years with single use. In the primary evaluable population (under 35 years, enrolled), the pregnancy rate was 10.3 (95% CI 5.4-19.9) per 100 woman-years with typical use, and 11.0 (95% CI 5.7-13.1) per 100 woman-years with single use. 90% of participants would choose or recommend it to others.
Fine (15) Retrospective Cohort UPA (48 hours - 120 hours)	The post-treatment pregnancy rate in the overall study population was 2.1% (95% CI 1.4-3.1%). The effectiveness did not decrease with increasing time: 48-72 hours: 2.3% (95% CI 1.4-3.8%); 72-96 hours: 2.1% (95% CI 1.0-4.1%); 96-120 hours: 1.3% (95% CI 0.1-4.8%).
Glasier (2010) (17) RCT UPA vs LNG	The pregnancy rate with UPA was 1.8% (95% CI 1.0-3.0), while with LNG it was 2.6% (95% CI 1.7-3.9, OR: 0.68, 95% CI 0.35-1.31).
Glasier (1992) (16) Mifepristone vs Yuzpe	The pregnancy rate with mifepristone was 0%, while with Yuzpe it was 1%.
Ho (18) RCT Yuzpe vs LNG (0,75 mgx2)	In Yuzpe method, treatment was ineffective in 2.6% of cases, while in LNG method it was ineffective in 2.4% of cases.
Kuchera (19) Retrospective Cohort Diethylstilbestrol	No pregnancies occurred during the study (among 1000 women).
Moreau (20) Phase III trial	The overall pregnancy rate was 1.9% (95% CI 1.3-2.5) in the study population. Obesity and additional unprotected intercourse during the cycle increased the pregnancy rate. Pregnancy rate for normal-weight women:

First author Study design Investigated preparation	Efficacy
UPA	1.3% (95% CI 0.9-2); obese women: 3% (95% CI 1.5-5.4); normal-weight women with additional unprotected intercourse: 5.9% (95% CI 2.4-11.7); obese women with additional unprotected intercourse: 8.3% (95% CI 0.2-38.5).
von Hertzen (21) RCT Mifepriston vs. LNG (2x0,75 mg and 1,5 mg)	The pregnancy rate was 1.5% (21/1359) for mifepristone, 1.5% (20/1356) for 1.5 mg LNG, and 1.8% (24/1356) for 2x0.75 mg LNG (the groups did not differ significantly). The relative risk of pregnancy was 0.83 (95% CI 0.46-1.5) for 1.5 mg LNG compared to 2x0.75 mg LNG, and 1.05 (95% CI 0.63-1.76) for mifepristone compared to LNG.
Polakow-Farkash (22) * Prospective cohort LNG vs. ethynodiol diacetate or desogestrel	-
Sääv (23)* Prospective cohort Mifepristone	The highest concentration of mifepristone in breast milk was observed 12 hours after drug intake. The decrease in mifepristone concentration takes about 7 days. The mifepristone concentration in milk was measured with a 200 mg dose. The milk-to-serum ratio of mifepristone ranged from <0.013:1 to 0.042:1 on day 3. The calculated relative infant dose was highest at 1.5%. Breastfeeding can be safely continued without interruption while taking mifepristone.
Shabaan (24)* RCT LNG and breastfeeding as a contraceptive method (LAM)	Compared to women using the LAM method alone, in the LAM+LNG group (where women received counseling on both LAM and post-event pills and were given a pack of LNG), significantly more women started using regular contraception within 6 months. Pregnancy occurred significantly more frequently in the LAM-only group (5%) compared to the 0.8% LAM+LNG group.
Szontagh (25) Clinical trial Dienestrol	No pregnancies occurred when 10 mg dienestrol was used after each intercourse for 50 menstrual cycles (10 subjects). No pregnancies occurred when 2.5 mg dienestrol + 0.2 mg ethinyl diacetate were used after each intercourse for 60 menstrual cycles (20 subjects). Menstruation mostly remained regular.

First author Study design Investigated preparation	Efficacy
(10 mg dienestrol vs. 2,5 mg dienestrol +0,2 mg ethylodiol-diacetate	Relatively low doses can effectively prevent pregnancy with few side effects.
Turok (2014) (26) Observational study Copper vs LNG	The 1-year cumulative pregnancy percentage was 6.5% with IUD and 12.2% with orally taken LNG.
Turok (2021) (27) RCT Copper vs LNG IUD	The pregnancy rate was 0.3% with LNG IUD and 0% with Copper IUD.
Van Santen (28) Retropective Cohort Yuzpe	The pregnancy rate was 1.2% (4/333).
Yuzpe (29) Retrospective Cohort Yuzpe	The pregnancy rate was 1.6% (11/692).
Zhou (30) Multicenter Retrospective Cohort Copper	Among the 999 cases examined, there were 2 pregnancies, resulting in a pregnancy rate of 0.2%.

4.1.5 The side effect profile of emergency contraception methods

Generally speaking, side effects of orally administered emergency contraception methods are mild and rare. The most common side effects include nausea, vomiting, headache, breast tenderness, and menstrual irregularities.

In the case of the Yuzpe protocol (not available in Hungary), the most common side effect is nausea (37-52%), followed by vomiting (21%) and breast tenderness (12%), while bleeding disorders occur in a small percentage of cases (28, 29). Dienesgestrol causes few side effects (nausea, chest discomfort in 6% of cycles) (25). For diethylstilbestrol, nausea occurs in 44% of cases, no side effects occur in 31.5% of cases, and the menstrual cycle does not change in 40% of cases (19). Similarly, nausea is the most common side effect for LNG (24). When comparing lower-dose (2x0.75 mg) LNG to higher-dose (1x1.5 mg) LNG, some studies report a higher occurrence of headaches, breast tenderness, and heavy menstrual bleeding with the higher dose (8), while others find no difference in the side effect profile (13). When LNG is administered multiple times within one cycle (up to six times), headaches occur in 15% of cases, while nausea and abdominal pain occur in 6% of cases (14). The most common side effect of UPA is headache (20%), followed by nausea (13.6%), menstrual disorders (10.1%), and abdominal pain (9.6%) (20). Mifepristone, either alone or in combination with tamoxifen, causes few side effects, and their frequency is quite similar (10). When using UPA, the side effects are distributed as follows: 9.5% headache, 9.2% nausea, 6.8% abdominal pain, 4.1% menstrual disorders, 3.5% dizziness, and 3.4% fatigue. The cycle length increased by an average of 2.8 days, while the duration of menstrual bleeding did not change (15).

When comparing LNG to the Yuzpe protocol, nausea, vomiting, and fatigue occur significantly more frequently with the Yuzpe protocol (18). Fewer side effects were reported with mifepristone compared to the Yuzpe protocol (nausea 40% vs. 60%, vomiting 3% vs. 17%), but menstrual disorders were more common with mifepristone (42% vs. 13%) (16). When comparing mifepristone to LNG, there is also no difference in the occurrence of side effects (21). When comparing UPA to LNG, nausea occurs slightly more frequently with UPA than with LNG (29% vs. 24%), but the frequency of other side effects is similar (11, 17).

In terms of side effect profiles, there is no difference among intrauterine devices (27, 30, 31). For Copper IUD, changes in bleeding pattern occurred in 32% of patients, and

specifically, spotting was observed with IUDs inserted during the ovulatory period (30). When comparing Copper IUD to LNG-containing IUD, there was no difference in the frequency of side effects (27). Compared to orally administered medications, intrauterine devices are associated with a higher percentage of irregular menstrual bleeding and abdominal pain (9).

Table 6 summarizes the side effects of emergency contraception.

Table 6. Side effects of emergency contraceptives (7)

First author Study design Investigated preparation	Side effect
Arowojolu (8) RCT LNG (2x0.75 vs 1.5 mg)	The high dosage (1.5 mg LNG) significantly caused more headaches, breast tenderness, and heavy menstrual bleeding in women.
Bhatia (9) Retrospective Cohort Copper vs LNG (2x0.75 mg)	The use of LNG had minimal side effects, with only 5.77% experiencing nausea. On the other hand, when using Copper, a higher percentage experienced side effects: irregular menstrual bleeding (12.5%) and abdominal pain (18.75%).
Changhai (10) RCT Mifepristone vs Mifepristone + Tamoxifen	The side effects in both groups were mild and rare.
Creinin (11) RCT UPA vs LNG	Nausea occurred slightly more frequently with UPA (29% vs. 24%), but the frequency of other side effects was similar.
D'Souza (31) RCT GyneFix vs Copper	There was no difference in side effects between the two groups, and the bleeding patterns (frequency, duration, amount, etc.) were similar for GyneFix and Copper.
Dada (13) RCT LNG (2x0,75 vs 1,5 mg)	The frequency of side effects did not differ between the two groups (~22% nausea, ~12.5% fatigue, ~12% headache, 9-10% dizziness, ~9% vomiting in both groups).
Festin (14) Multicenter Prospective Cohort	Side effects: 3 serious adverse events, 102 milder, mild side effects (headache, nausea, abdominal and pelvic pain). One case of severe anemia.

First author Study design Investigated preparation	Side effect
1,5 mg LNG after each intercourse (up to a maximum of 6 times per month) Phase III trial	
Fine (15) Retrospective Cohort UPA (48 hours - 120 hours)	Side effects reported were: headache 9.5%, nausea 9.2%, abdominal pain 6.8%, menstrual irregularities 4.1%, dizziness 3.5%, and fatigue 3.4%. The average cycle length increased by 2.8 days, while the duration of menstrual bleeding did not change.
Glasier (2010) (17) RCT UPA vs LNG	The most common side effect was headache (19.3% with UPA, 18.9% with LNG). Severe dizziness occurred in one case with UPA, and one case of molar pregnancy was reported with LNG.
Glasier (1992) (16) Mifepristone vs Yuzpe	Fewer side effects were reported with mifepristone compared to Yuzpe (nausea 40% vs. 60%, vomiting 3% vs. 17%), but menstrual disturbances were more common with mifepristone (42% vs. 13%).
Ho (18) RCT Yuzpe vs LNG (0,75 mgx2)	Nausea, vomiting, and fatigue occurred significantly more frequently with Yuzpe compared to LNG.
Kuchera (19) Retrospective Cohort Diethylstilbestrol	44% of participants experienced nausea, 31.5% did not experience any side effects at all, and 40% did not have any changes in their menstrual cycle.
Moreau (20) Phase III trial UPA	The most common side effects were headache (20%), nausea (13.6%), menstrual irregularities (10.1%), and abdominal pain (9.6%).
von Hertzen (21) RCT	The occurrence of side effects did not differ between the groups. Menstrual bleeding occurred earlier with LNG compared to mifepristone.

First author Study design Investigated preparation	Side effect
Mifepriston vs. LNG (2x0,75 mg and 1,5 mg)	
Polakow-Farkash (22) * Prospective cohort LNG vs. ethynodiol diacetate or desogestrel	Maternal side effects: menstrual irregularities occurred less frequently with LNG treatment. Decreased lactation was not common and similar in both groups.
Sääv (23)* Prospective cohort Mifepristone	-
Shabaan (24)* RCT LNG and breastfeeding as a contraceptive method (LAM)	Minimal side effects were reported with LNG use (nausea (28.8%), vomiting (2.9%)).
Szontagh (25) Clinical trial Dienestrol (10 mg dienestrol vs. 2,5 mg dienestrol +0,2 mg ethylodiol-diacetate	10 mg dienestrol caused few side effects (nausea). The regularity of the menstrual cycle depended on the frequency of intercourse (10 mg dienestrol had to be taken after each intercourse). 2.5 mg dienestrol + 0.2 mg ethinyl diacetate: moderate nausea, chest discomfort (in 6% of cycles).
Turok (2014) (26) Observational study Copper vs LNG	-
Turok (2021) (27) RCT Copper vs LNG IUD	Side effects were reported in 17 cases (5.2%) with LNG IUD and 16 cases (4.9%) with Copper IUD.

First author Study design Investigated preparation	Side effect
Van Santen (28) Retropective Cohort Yuzpe	The most common side effect was nausea (37%), followed by vomiting (21%). 12% of patients reported breast tenderness. 75% of the side effects resolved within one day. Only 15% of patients reported side effects on the third day compared to intake.
Yuzpe (29) Retrospective Cohort Yuzpe	42% of patients had no side effects, 51.7% reported nausea, and other side effects (breast pain 0.6%, abnormal bleeding 0.3%) occurred in a small percentage.
Zhou (30) Multicenter Retrospective Cohort Copper	Two expulsions occurred during the study. Changes in bleeding pattern were reported by 32% of patients, specifically with spotting during the ovulation period for IUDs inserted during that time. 93% of patients requested continued use of the IUD for ongoing contraception.

4.1.6. The weight as a factor influencing decision-making

The intake of levonorgestrel preparations is not recommended for individuals with a body weight of 75 kg or a BMI of 25 and above. In such cases, the German guidelines recommend the use of UPA (11). In individuals with a BMI of 30 and above, the use of UPA was associated with a twofold increase in the likelihood of pregnancy (20). Moreover, if there were multiple unprotected intercourse events during the menstrual cycle, obese women had a fourfold increase in the rate of pregnancy (20).The efficacy of orally administered contraceptives is lower in women with higher body weight compared to what is observed with intrauterine devices, with the latter being the safest method in this specific population group (32). Table 7 summarizes the influencing role of body weight and BMI in the choice of emergency contraception.

Table 7. The influence of body weight and BMI on the choice of emergency contraception (7)

First Auther	Active substance	Study design (number of patients)	Summary
Creinin (11)	LNG vs UPA	RCT (n=773)	The risk of pregnancy increases above 70-75 kg, and for those weighing 80 kg or more, the risk of pregnancy is 6% or higher.
Glasier (17)	LNG vs UPA	RCT (n=2221)	For individuals with a BMI over 25, UPA (ulipristal acetate) or IUS (intrauterine system) is recommended instead of LNG (levonorgestrel) preparations.
Moreau (20)	UPA	Prospective, multicenter (n=2183)	For those weighing 85 kg or with a BMI over 30, there is a twofold increase in the risk of pregnancy, which is not dependent on the speed of drug intake.

4.1.7. Breastfeeding

Levonorgestrel preparations can be safely used during breastfeeding, as the clinically insignificant amount of the active ingredient is excreted into breast milk (22). Breastfeeding as a contraceptive method (Lactational Amenorrhea Method, LAM) supplemented with LNG counseling and LNG tablets (as needed) resulted in significantly more women starting regular contraception within 6 months compared to women using only the LAM method. Pregnancy occurred significantly more frequently in the LAM-only group (5%) compared to the 0.8% in the LAM+ LNG group (24). In the case of mifepristone, the highest concentration of the drug in breast milk was observed 12 hours after drug intake. The calculated relative infant dose was 1.5%, indicating that breastfeeding can safely continue without interruption when using mifepristone (23).
Table 8 summarizes the effects of emergency contraceptives on breastfeeding and milk production.

Table 8.: Effects of emergency contraceptives on breastfeeding and milk production (7)

First Auther	Active substance	Study design	Breastfeeding	Side effect	Limitation
Polakow-Farkash (22)	Levonorgestrel 1.5 mg	Prospective observational cohort study (n=143)	Breast milk production was not significantly reduced.	-	There is none
Sääv (23)	Mifepristone 200 mg /600 mg	Comparative study (n=12)	-	There is none	There is none, particularly at a dose of 200 mg.
Shabaan (24)	Levonorgestrel 1.5 mg	RCT (n=1158)	Unchanged	Unchanged Nausea (28.8%, vomiting 7%)	There is none

4.2. Retrospective observational study - Motivators for emergency contraception

4.2.1. Description of the sample of the Hungarian database

Table 9 displays the characteristics of the participants. Among the 455 patients, 30 was the median age (interquartile range: 25–37). 14 hours was the median amount of time that had passed since the sexual contact (interquartile range: 5-32). 14 days was the median number of days since the start of the most recent menstrual cycle (interquartile range: 10.75-19.92).

Out of all the patients, 59.3% (n = 270) reported condom breakage, 29.5% (n = 134) reported no protection, and 11.2% (n = 51) reported other reasons; 74.1% (n = 337) of the patients had no prior pregnancy history, 25.9% (n = 118) had been pregnant before, and 5.5% (n = 25) of the patients had had at least one abortion. In total, 29.9% (n=136) claimed having a one-night stand, whereas 70.1% (n=319) stated being in a relationship.

Table 9. Characteristics of the sample (33)

Characteristics	N (range or %)
Total	455 (100%)
Age (years)	30 (25-37)
Relationship status	
In relationship	319 (68.6%)
No relationship	136 (31.4%)
History of prior pregnancies	
Pregnancy (n)	118 (25.9%)
Never pregnant	337 (74.1%)
Proximity to ovulation in the cycle	
Median number of days	14 (11-20)
12-16 days (n)	130 (28.6%)
<12; 16<	325 (71.4%)
Hours since last intercourse	14 (5-32)
Method of contraception	
Condoms	270 (59.3%)
No contraception	134 (29.5%)
Other	51 (11.2%)

Categorical parameters are presented as n. Continuous data are presented as median (interquartile range).

4.2.2. Relationship between time since intercourse and patient characteristics

Those who had used condoms registered after a significantly shorter time than those without protection (p=0.032) or those using another type of protection (p=0.048, **Figure 2**).

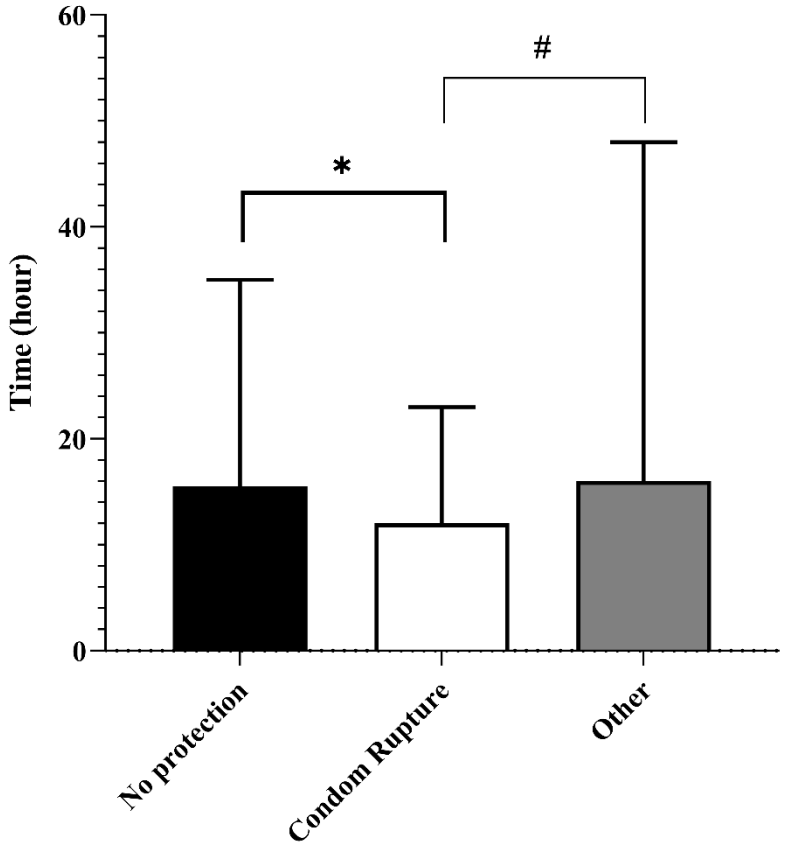

Figure 2. Protection strategy in respect to the amount of time since the last sexual encounter. The no-protection group had a considerably longer time elapsed since their last sex than the condom rupture group. Additionally, compared to the patient group using alternative protection techniques (such as coitus interruptus), this duration was substantially shorter in the condom rupture group. The interquartile range and median are displayed for the data. Dunn's post hoc test combined with the Kruskal-Wallis test. *p=0.032 Condom Breakage vs. No Defense; #p=0.048 Condom Breakage vs. Additional (33).

Furthermore, patients with a history of prior pregnancy also showed a substantially shorter elapsed time (p=0.004). **(Figure 3)**.

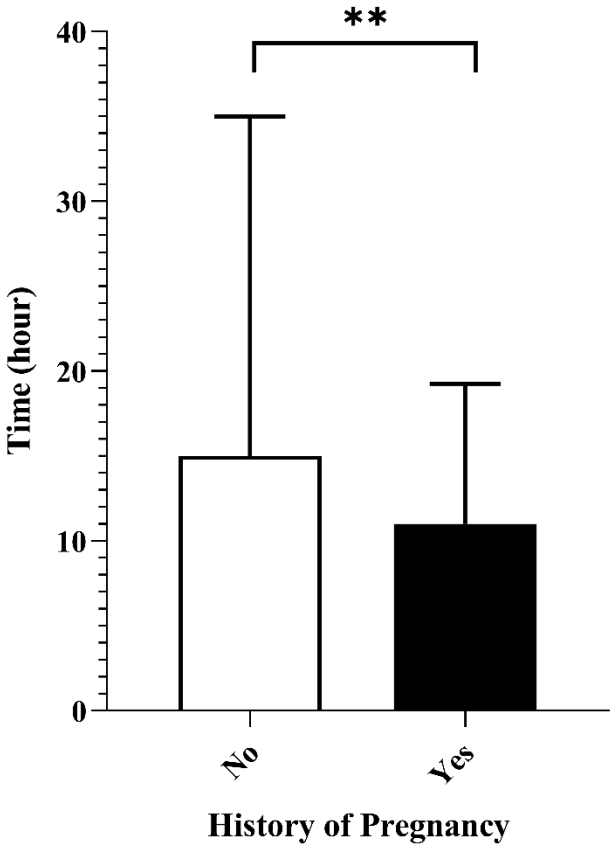

Figure 3. The sample was distributed based on prior pregnancy history as a means of encouraging early application of emergency contraceptives. Less time passed for patients who had previously given birth as opposed to those who had never given birth. The interquartile range and median are displayed for the data. Mann-Whitney test: **p=0.0052 prior pregnancy history compared to no prior pregnancy history (33).

Age, relationship status, menstrual cycle proximity to ovulation, and duration since last sex did not significantly correlate with each other. **(Table 10)**.

Table 10. Relationship between time since intercourse and patient characteristics (33)

Characteristics	Median time (SE)
Age	
< 30 (n=216)	14.5 (1.6)
> 30 (n=239)	13.0 (1.4)
Mann-Whitney p-value	0.8596
Relationship status	
In relationship (n=319)	13 (1.3)
Not in relationship (n=136)	15 (2.0)
Mann-Whitney p-value	0.1042
Proximity to ovulation in cycle	
Ovulation (12-16) (n=130)	13.5 (1.8)
Before ovulation (<12) (n=167)	14.0 (1.7)
After ovulation (16<) (N=158)	14.0 (1.7)
Kruskall-Wallis p-value	0.771

4.2.3. Relationship between patient features and contraceptive methods

Age, marital status, the time of cycle's ovulation, and the history of previous pregnancies did not correlate with the type of contraception used.

4.2.4. Multivariable logistic regression model of factors impacting EC requests

A multivariate logistic regression analysis was performed to determine the probability of an EC request. Time was a dependent variable; if patients registered on the website within 24 hours, it received a value of 1, and if it took longer than 24 hours, it earned a value of 0. Protection (yes/no), ovulation time, past pregnancy history (yes/no), relationship status (yes/no), and age were the independent factors. Only protection (yes/no) and pregnancy history (yes/no) were significant independent factors. *(**Table 11**)*.

Table 11. Relationship between methods of contraception and patient characteristics (33)

Relationship status		
	Condom Rupture+Other (n)	**No Protection (n)**
Relationship	225 (70.5%)	94 (29.5%)
No Relationship	96 (70.6%)	40 (29.4%)
Chi-square p-value	0.920	
Proximity to ovulation in cycle		
	Condom Rupture+Other (n)	**No Protection (n)**
12-16 days (n)	82 (63.1%)	48 (36.9%)
<12; 16< (n)	239 (73.5%)	86 (26.5%)
Chi-square p-value	0.036	
History of prior pregnancies		
	Condom Rupture+Other (n)	**No Protection (n)**
Pregnancies	83 (70.3%)	35 (29.7%)
No pregnancies	238 (70.6%)	99 (29.4%)
Chi-square p-value	0.953	
Proximity to ovulation in cycle – in relationship (n=319)		
	Condom Rupture+Other (n)	**No Protection (n)**
12-16 days (n)	52 (64.2%)	29 (35.8%)
<12; 16< (n)	173 (72.7%)	65 (27.3%)
Chi-square p-value	0.191	
Proximity to ovulation in cycle – not in relationship (n=136)		
	Condom Rupture+Other (n)	**No Protection (n)**
12-16 days (n)	20 (64.5%)	11 (35.5%)
<12; 16< (n)	76 (72.4%)	29 (27.6%)
Chi-square p-value	0.535	

The logistic model analysis also showed that the use of any form of protection (condom, withdrawal, or other) significantly increased the risk of EC request (odds ratio = 1.757, 95% confidence interval: 1.137-2.715; p=0.011). Furthermore, a prior pregnancy also significantly increased the risk of EC request (odds ratio = 1.858, 95% confidence interval: 1.063-3.248; p=0.03). **Figure 4, Figure 5**).

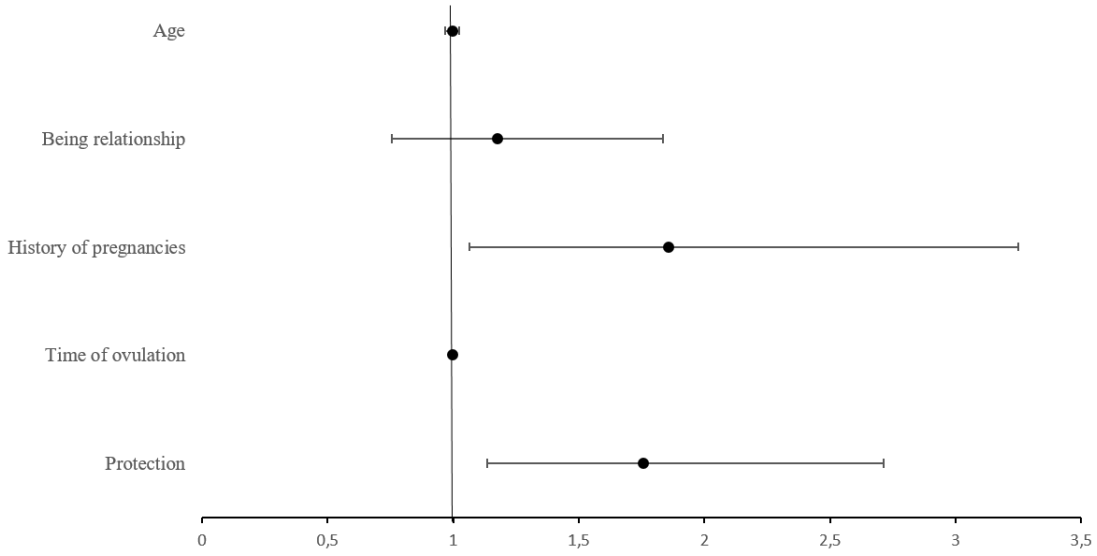

Figure 4. A forest plot showing odds ratios at the EC's request. A logistic model analysis revealed that the risk of EC request was significantly increased by using any form of protection (condom, interrupt sex, and other) (odds ratio = 1.757, 95% confidence interval: 1.137-2.715; p=0.011); additionally, the risk of EC request was significantly increased by pregnancy at an earlier age (odds ratio = 1.858, 95% confidence interval: 1.063-3.248; p=0.03) (33).

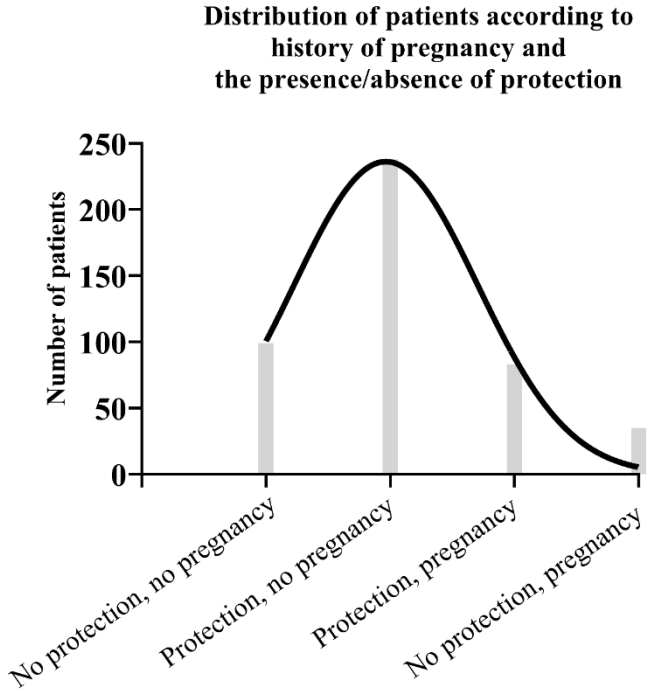

Figure 5. The distribution of patients with a history of prior pregnancy as well as the use of protection (33).

5. DISCUSSION

5.1. The problem of unintended pregnancy

In 2012, there was a recorded total of 213 million pregnancies, showing a marginal increase from the 211 million pregnancies reported in 2008. The global pregnancy rate experienced a minor decrease during the 2008-2012 period, following a significant decline observed between 1995 and 2008. Out of the total pregnancies in 2012, a substantial 85 million, equivalent to 40 percent, were unintended. Among these unintended pregnancies, 50 percent concluded with an abortion, 13 percent ended in miscarriage, and 38 percent resulted in an unplanned birth (34).

Emergency contraception serves as a preventive measure to significantly reduce the occurrence of unintended pregnancies resulting from contraceptive failure or unplanned sexual encounters. This intervention plays a crucial role in minimizing the risks associated with unsafe abortions, thereby contributing to the reduction of maternal mortality and morbidity. Indeed, the implementation of emergency contraception has led to a notable reduction in the proportion of maternal mortality attributed to unsafe abortions, decreasing from 13 percent to 8 percent since its introduction (4). But it is very important to mention that the use of emergency contraceptives does not replace primary prevention.

In addition to regular contraception, emergency contraceptives also protect against unwanted pregnancy. There are oral emergency contraceptives that contain hormones such as levonorgestrel (35) or ulipristal acetate (36), and the Copper IUD can also be used as an emergency contraceptive method, which is hormone-free (37).

Many epidemiological factors play a role in which option women choose in this situation. The decision can be influenced by previous experience, general knowledge about contraceptives, advice from friends, availability, etc. (38) A limitation in the mapping of these factors is that little data is available, and few comprehensive, detailed, all-encompassing studies have been prepared over the years.

This thesis provides a comprehensive answer to the uncertainty and questions that arise during emergency contraception.

5.2. The presence of emergency contraceptives

The first studies regarding reliable post-event contraception began in the 1970s. The initial research was conducted using diethylstilbestrol (DES), a synthetic estrogen, which exerted its effects by inhibiting implantation (19). Studies on the use of post-event contraception also began in Hungary during this time, as evidenced by the investigation of the efficacy of another synthetic estrogen, dienestrol, as a post-event contraceptive by Szontagh FE and Kovács L in 1969 (25). In a clinical study involving 30 participants, neither low nor high doses of dienestrol resulted in pregnancy during the study period (25). In 1985, the United States Food and Drug Administration (FDA) declared DES as carcinogenic, leading to its withdrawal from the market in 2000 (39).

Yuzpe, a Canadian physician, was the first to use high-dose combined oral contraceptives containing estrogen and synthetic progestogen for the purpose of preventing unwanted pregnancies, and this method was later named after him (29, 40). The administration regimen involved taking 200 micrograms of ethinylestradiol and 2 mg of dinorgestrel, which was later reduced to 1 mg of levonorgestrel (LNG). The drugs were taken in repeated doses with a 12-hour interval, up to a maximum of 72 hours following unprotected sexual intercourse (41). In the Yuzpe method, the contraceptive effect is achieved by either delaying ovulation or reducing endometrial receptivity, based on the timing relative to the menstrual cycle. If implantation has already occurred, the mentioned hormones are not harmful to pregnancy and do not induce miscarriage. The success of the Yuzpe method was overshadowed by the side effects associated with the high-dose estrogen component (headache, nausea, vomiting, breast tenderness), leading to the testing of progestin-only post-event contraceptives since the 1980s to minimize these effects (18, 28). In 1997, the World Health Organization (WHO) conducted a multicenter study comparing progestin-only preparations with the previously used Yuzpe method. The study found lower pregnancy rates and a more favorable side effect profile, but the time elapsed since the event was identified as the most influential factor for success in both methods (41-43). In Hungary, there is no commercially available product equivalent to the Yuzpe method.

In Eastern countries (Russia, Vietnam, China), mifepristone (a progesterone receptor antagonist) is also used as emergency contraception (18, 44). A multicenter clinical trial found no significant difference between different doses (600 mg vs. 50 mg vs. 10 mg)

(45). Its use as emergency contraception is permitted in lower doses (25-50 mg) compared to the dosage required for medication-induced abortion (21). Further investigating its efficacy, a randomized controlled trial published in 2002 found no significant difference in effectiveness when mifepristone was combined with tamoxifen (10). The use of mifepristone as a post-coital contraceptive has not become established in Europe and the USA.

When levonorgestrel preparations were introduced, the initial protocol involved taking two doses of 0.75 mg with a 12-hour interval. Subsequent studies have shown that the side effect profile and effectiveness remain unchanged when the full dose is taken at once, leading to the development of single-dose preparations (8, 13, 21). The efficacy, safety, and applicability of LNG were previously investigated as a contraceptive drug for women with infrequent sexual activity (less than six times per month), with the participation of the WHO Center in Szeged. When 1.5 mg of LNG was administered before or after sexual intercourse, the pregnancy rate was 4.4% in typical use (14). LNG preparations are well-tolerated and widely available, but their use is limited by the 72-hour timeframe for administration.

Ulipristal acetate (UPA) is the first selective progesterone receptor modulator (SPRM) specifically approved for emergency contraception by the FDA under the name EllaOne® in 2010 (17). Unlike previous preparations, UPA can be administered as a single dose up to 120 hours (5 days) after unprotected sexual intercourse (15). In Hungary, similar to LNG, UPA is also available by prescription.

Copper intrauterine devices (IUDs) provide safe and effective protection against unwanted pregnancy. Their use as emergency contraception is accepted within 5 days of the event, even without FDA approval (26, 46). This method can be particularly useful for women in stable relationships who seek reliable and long-term contraception beyond emergency use (9, 15, 30).

Due to a lack of comprehensive studies, clinical data is not available regarding the use of levonorgestrel-releasing intrauterine systems (LNG-IUS) or other non-hormonal intrauterine devices approved for long-term contraception, such as Gynefix (27, 31).

5.2.1. Mechanism of action of emergency contraceptives used in Hungary

Levonorgestrel is a synthetic progestogen that does not affect the "first-pass" mechanism, resulting in a bioavailability of nearly 100%. Its binding to sex hormone-binding globulin (SHBG) and albumin is very high, and its metabolites are excreted in urine and feces. It reaches peak plasma concentration within 1.7 hours and has a half-life of 27.5 ± 5.6 hours (47).

In addition to levonorgestrel, ulipristal acetate is also an orally administered emergency contraceptive, taken as a single dose of 30 mg. It is rapidly absorbed, reaching peak concentration in the blood within 0.5-3 hours after administration (48). The effectiveness of these drugs is not influenced by food intake.

While a product specifically corresponding to the Yuzpe protocol is not available in Hungary, it is worth mentioning for completeness that the Yuzpe protocol involves taking increased doses of regular contraceptive pills containing both estrogen and levonorgestrel components. The estrogen component should contain a minimum of 100-120 μg of ethinylestradiol, and the progestogen component should contain either 0.50-0.60 mg of levonorgestrel or 1.0-1.2 mg of norgestrel (40).

The common characteristic of emergency pills is that they exert their effects by inhibiting ovulation and interfering with the functions of the luteal phase (such as endometrial receptivity and thickening). Levonorgestrel increases the viscosity of cervical mucus, reduces its quantity, and alters its biochemical composition, thereby impeding the movement of spermatozoa (49, 50). Ulipristal acetate can delay the peak of luteinizing hormone (LH), which triggers ovulation, by 24-48 hours, potentially preventing follicle rupture (51). By inhibiting endometrial maturation, UPA also hinders implantation, and this effect has been confirmed by endometrial biopsies conducted during the luteal phase following the administration of 50 and 100 mg doses (52). Common side effects of emergency contraceptive pills may include nausea, vomiting, fatigue, breast tenderness, and irregular menstrual bleeding. These side effects are typically transient and will subside on their own.

5.2.2. Efficacy and side effect profile of emergency contraception methods

In the studies we included, intrauterine contraceptive devices (as a form of emergency contraception) were either equally effective (9) as LNG or more effective than it (0.2%

pregnancy rate for Copper IUD (30), cumulative one-year pregnancy percentage of 6.5% for Copper IUD compared to 12.2% for orally administered LNG (26)). There is no difference in efficacy between LNG IUD and traditional copper-containing IUD (Copper) (27). The efficacy of GyneFix is similar to Copper, but it causes less abdominal pain (31). Compared to all orally ingestible pills, copper-containing IUD clearly proves to be the most effective emergency contraceptive method, with nearly 100% efficacy (53). Its advantage is that it can be used as a long-term contraceptive method in addition to resolving urgent situations, making it both convenient and cost-effective. A previous study showed that 80% of patients continued to use the inserted device as their primary contraceptive method (54). According to a meta-analysis published in 2022, LNG-IUS can be safely and effectively used as an emergency contraception method (33). In a systematic review published in 2017 by Cochrane, which examined orally administered medications, the least effective treatment was the Yuzpe method. It was followed in terms of safety by the LNG preparation, which was surpassed in efficacy by moderate-dose (25-50 mg) mifepristone and UPA (55).

The Cochrane review published in 2017 also summarized the side effect profile of emergency contraception methods (55). Similar to our findings, the study found that the most common side effects of emergency contraceptives are nausea and vomiting. The review demonstrated that LNG had the least delaying effect on menstruation (6%), while UPA most commonly caused menstrual irregularities and shifts in the timing of menstruation (20%). Copper IUD can be associated with side effects typical of intrauterine devices, with lower abdominal pain being the most pronounced. In terms of side effects, the Yuzpe protocol was the least favorable (42%), with the most common complaints being nausea and vomiting (41).

The main limitation of emergency contraceptive pills is that their effectiveness is achieved with a single use. In cases of repeated intercourse in short intervals, continuous contraception (COC, IUD) is recommended.

5.2.3. Emergency contraception and breastfeeding

For breastfeeding mothers, the use of an IUD is particularly recommended if they wish to switch to long-term contraception after the emergency situation has passed. LNG-

containing intrauterine devices can also be used during breastfeeding. Due to its strong plasma protein binding, ulipristal acetate is detected in very low concentrations in breast milk. Consequently, the transfer to the infant is minimal, and gastrointestinal absorption in the infant is even lower due to the high fat content of breast milk. Recommendations regarding the duration of suspension of breastfeeding vary. The World Health Organization (WHO) supports the continuation of breastfeeding, while the Centers for Disease Control and Prevention (CDC) in the United States advocates suspending breastfeeding for 24 hours. However, the drug's usage guidelines suggest an 8-hour suspension (56).

5. 3. Retrospective observational study in Hungary

The MEEC cohort study represents the inaugural research endeavor to investigate the potential influence of epidemiological factors, such as pregnancy prevention methods, age, relationship stability, pregnancy and abortion history, and knowledge of ovulation, as driving forces behind the utilization of emergency contraception (EC).

In our study, we found compelling evidence highlighting the prominent impact of condom breakage/condom usage and the history of prior pregnancies as the most influential factors driving the use of emergency contraception (EC). Our research also confirmed the presence of insufficient education, indicating an information gap within this specific population. Interestingly, despite efforts to prevent pregnancy, we did not observe a clear correlation between the examined epidemiological factors and the methods employed for protection during sexual intercourse. This observation held true, particularly when considering the timing of ovulation as a critical variable.

Condoms have gained significant popularity and are widely regarded as one of the most prevalent methods of contraception. (57-60). In addition to their primary function of preventing pregnancy, condoms also serve as an effective means of safeguarding against sexually transmitted diseases (STDs) (61). Contrary to pharmaceutical companies in Hungary, condom makers have widespread popularity and can readily advertise their products, expanding their customer base. Five independent studies conducted in the United Kingdom on the effectiveness of condom use found an average failure rate (Pearl Index) of 3.26/100 (62). The Pearl Index for condoms is substantially lower than that of hormonal contraceptives (0.6 for LNG-IUDs and 1.85 for oral contraceptives,

respectively). Therefore, using condoms to prevent an unwanted pregnancy may give rise to a false sense of security (63-65). Our research unequivocally demonstrated that the use of emergency contraception was frequently motivated by condom rupture. Ensuring that couples utilize an acceptable, safe, and effective method of contraception is largely dependent on providing adequate patient education. Encouraging contraceptive options with a Pearl Index greater than a condom may contribute to a decrease in the frequency of unwanted births and the use of morning-after medications.

In the postpartum period, women's knowledge of unplanned pregnancies is comparatively low, and it is strongly impacted by sociodemographic characteristics such as gravidity, household income, and educational attainment (66). Goldsmith et al. found that raising women's knowledge could help postpartum women avoid unwanted pregnancies after analyzing 1,795 survey charts (67, 68). Our research revealed that one of the main driving forces behind the use of EC following an inadequately protected sexual encounter was a prior pregnancy. This begs the question of whether patient education in Hungary during the postpartum period is acceptable, since it is likely possible to prevent the stressful scenario of having emergency contraception. During breastfeeding, progesterone-only pills (which have a usual failure rate of 7) or intrauterine devices (which have a typical failure rate of 0.7) are very effective methods of contraception (69). As a first-choice long-acting reversible contraceptive (LARC) for women, IUDs may be taken into consideration (70, 71). A stronger focus on suitable patient education regarding LARC may discourage postpartum women from utilizing emergency contraceptives and encourage them to choose safer alternatives.

We also looked at the relationship between epidemiological factors and preventative measures. Our research found no link between the stability of the relationship or the use of any form of contraception and abortion in the medical history. Furthermore, despite the clear goal of preventing pregnancy, there was no discernible difference between the protection strategies (condom use vs. no protection) and the timing of ovulation. It is obvious that there is a lack of patient awareness given the lack of meaningful differences. In their 2015 investigation, Hampton et al. reached a similar conclusion (72). It was evident from their findings that less than one-third of women could accurately determine whether they were at a fertile phase of their cycle, indicating a severe lack of knowledge about fertility.

The International Glossary on Infertility and Fertility Care defines fertility awareness as "the understanding of reproduction, fecundity, fecundability, and related individual risk factors: advanced age, sexual health factors, such as STDs, and lifestyle factors, such as smoking, obesity, and work place factors; including the awareness of societal and cultural factors affecting options to meet family planning needs and reproductive family planning" (73).

Pedro et al. included 71 studies exploring fertility awareness in their systematic review. They found that fertility awareness among people in the reproductive age was low to moderate, even age did not seem to have an important role. The evidence suggested that women, more educated people, people bearing infertility, had greater fertility awareness levels. Having or desiring to have children was not related to fertility awareness levels (74). Their conclusions support those of our investigation.

In general, Europe has a low fertility rate—none of its nations have fertility rates higher than 2.0. In 2020, Hungary's fertility rate was 1.52, which indicates that the majority of women do not become mothers twice in their lives (75). Hungary should prioritize raising fertility awareness among its youth in order to close the gap between the number of children desired and the actual fertility rate.

6. CONCLUSIONS

Our experiments focused on the following questions:

1) The sistematic summarize information based on the literature data regarding the evidence-based modern methods, effectiveness, and practical application of emergency contraception in order to reduce the occurrence of unintended pregnancies.

Emergency contraception is designed for individuals who have had unprotected sexual intercourse, encountered contraceptive mishaps, or found themselves in situations where regular birth control was not utilized. Based on the 23 studies included in the literature research, the most frequently used method is the pill containing levonorgestrel, which is also confirmed by Hungarian data. In addition to LNG, UPA is also used as an emergency contraceptive in Hungary, while mifepristone and the Copper-IUD are also used in international practice. It is important to note that the most commonly used emergency contraceptive worldwide is the LNG-containing pill, however, the copper IUD has been shown to be more than 99% effective in preventing pregnancy. Regarding their side effects, there is no significant difference between the different methods, the most common side effects are nausea, headache and lower abdominal pain.

2) The elucidation and comprehension the factors that promote women to seek emergency contraception immediately after intercourse

Women who possess comprehensive knowledge regarding emergency contraception and its accessibility are more inclined to promptly seek it following unprotected intercourse. Being aware of the time-sensitive nature of emergency contraception and its effectiveness can motivate women to take immediate action. Women who have encountered contraceptive failures, like condom rupture or have previous experiences with emergency contraception are more likely to promptly seek it in future instances of unprotected intercourse. The time is also influenced by the previous pregnancy, because women with a history of pregnancy applied more quickly for emergency contraception. Establishing a

supportive and open line of communication with sexual partners can have a positive influence on a woman's determination to seek emergency contraception promptly. Partner encouragement to prioritize reproductive health and overall well-being can play a substantial role in this decision-making process.

Individuals who used condoms as a contraceptive method showed a significantly shorter time interval before seeking emergency contraception compared to those who did not use any form of protection or used alternative protective methods. Furthermore, patients with a prior history of pregnancy exhibited a notably reduced elapsed time before seeking emergency contraception.

7. SUMMARY

Introduction: Emergency contraception offers a reliable and secure means of preventing unintended pregnancies. There exists a range of available methods for emergency contraception, each employing distinct mechanisms of action and timeframes.

Objectives: In this thesis, I would like to investigate and summarize the information on the populations, evidence-based modern methods, effectiveness, and practical application of emergency contraception. The retrospective cohort study explores the motivating circumstances to use emergency contraceptives as fast as possible.

Methods: In the systematic review to gather relevant information, we performed a comprehensive literature search across prominent databases including MEDLINE (PubMed), Embase, and Scopus. In the retrospective observational study utilized data from a Hungarian database comprising follow-up information from women who sought emergency contraception via telemedicine consultations. The study assessed various variables, including age, gynecological history, details of the sexual intercourse, menstrual cycle data, and relationship status.

Results: Based on the literature, our publication provides guidance for the selection of available emergency contraceptives in Hungary, taking into account factors such as effectiveness and accessibility, while emphasizing collaboration with potential users. Individuals who used condoms as a contraceptive method showed a significantly shorter time interval before seeking emergency contraception compared to those who did not use any form of protection or used alternative protective methods. Furthermore, patients with a prior history of pregnancy exhibited a notably reduced elapsed time before seeking emergency contraception.

Conclusion: Our study findings emphasize the considerable influence of condom rupture and prior pregnancy history as the most significant motivating factors for emergency contraception utilization. Additionally, our research sheds light on the insufficient awareness of fertility awareness methods in Hungary. We strongly suggest that healthcare authorities support the creation of updated clinical guidelines, aiming to enhance the accessibility of emergency contraception and promote improved reproductive health outcomes.

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